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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Fulbright & Jaworski L.L.P.
Market Square
801 Pennsylvania Avenue, N.W.
Washington, DC 20004-2623

EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,472	MA ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 28-31* is/are pending in the application.

4a) Of the above claim(s) *5-27 and 32-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Claims 1-44 are pending, and claims 5-27 and 32-44 have been withdrawn from consideration as being directed to a non-elected invention.

2. Claim 1-4 and 28-31 are under examination.

3. Applicant's election with traverse of Group I, claims 1-4 and 28-31, in the reply filed on January 12, 2006 is acknowledged. The election is treated as an election without traverse because Applicant did not indicate any errors in the restriction requirement. The restriction requirement is deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4 and 28-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not

'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to the following:

an isolated peptide consisting of an amino acid sequence selected from the group consisting of ALKVEERX (SEQ ID NO:1), wherein X may be an amino acid (claim 1), wherein X is Ala, Val, Leu, Ile, Pro, Phe, Met, Trp or Glu (claim 2), wherein the peptide consists of the amino acid sequence selected from the group consisting of SEQ NO:3 and SEQ ID NO:5 (claim 3),

and

a composition useful in provoking a cytolytic T cell response comprising the isolated peptide of claim 1, and an adjuvant (claim 4),

and

an isolated complex useful in isolating a cytolytic T cell, comprising a first and second binding partner which are specific for each other, wherein said second binding partner is bound a plurality of tetramers of an HLA-A2 molecule, a β_2 microglobulin molecule, and the peptide of claim 1 (claim 28), further comprising a label (claim 29), wherein said first binding partner is avidin and the second binding partner is biotin (claim 30),

and

a composition comprising the tetramer of claim 28 and a carrier (claim 31).

The specification teaches that a cytotoxic T lymphocyte (CTL) was identified by establishing a melanoma tumor cell line, EB81-MEL.2, from a patient EB81, coculturing the tumor cell line with lymphocytes from the patient, and identifying the CTL clone 606 C/22.2 which lyses the EB81-MEL.2 cell line, by limiting dilution (page 40, lines 8-20). The specification teaches that patient EB81 had been vaccinated with DNA vaccine encoding a MAGE-1 peptide and a MAGE-3 peptide, and with the peptides, wherein the peptides are unrelated to the MAGE-C2 peptide described below (page 42, lines 4-9), and that the CTL clone did not recognize cells pulsed with the peptides used for vaccination (page 40, lines 13-20). The specification also teaches that the gene encoding the antigen was identified as MAGE-C2 by preparing a plasmid cDNA library from mRNA isolated from the EB81 melanoma patient, transfecting cells with the library to form a library of transfected cells, adding the CTL clone to the transfected cells, and identifying reactivity via measurement of TNF production (page 40, lines 21-29). The specification teaches that the newly isolated MAGE-C2 cDNA differed from previously described MAGE-C2 cDNAs by the presence of short intronic sequence that is not splice out that is located in the 5'-untranslated region of the gene and does not affect the coding region (page 41, lines 1-7). The specification teaches that the reactive portion of the MAGE-C2 antigen was identified by constructing minigenes of MAGE-C2 cDNA, transfecting cells with the minigenes, and identifying reactivity via TNF production, wherein it was determined that the peptide was encoded with the last 211 nucleotides of the open reading frame of the MAGE-C2 DNA (page 41, lines 14-18). The specification teaches that several candidate peptides bearing the binding motif for HLA-A2 were synthesized, and the nona-peptide ALKDVEERV (SEQ ID NO:3) was found to stimulate TNF release by cells of the CTL clone (page 41, lines 14-18). The specification further teaches that recognition of the peptide of SEQ ID NO:3 was confirmed by a lysis assay of autologous EBV transformed EB81 lymphocytes cells pulsed with the peptide (page 41, lines 14-24). The specification also teaches that the frequency of CTL 606C/22.2 cells to CD8 cells was determined in samples of PBMCs

and in melanoma tumor samples from patient EB81, with frequencies of cells of $4x10^{-5}$ and 10^{-1} thru 10^{-2}, respectively, thus indicating an enrichment of the CTL cells in the tumor sample versus the PBMCs (page 43, lines 10-33). The specification also teaches that a series of allogeneic HLA-A2 tumor lines were tested and several were recognized by the identified CTL clone, as determined using a TNFα production assay, including AVL3-MEL, LB373-MEL, and myeloma U266 (page 40, lines 16-19). The specification references Lucas et al. (2000, Int. J. Cancer 87:55-60), Gure et al. (2000, Int. J. Cancer 85:726-732), and U.S. Patent No. 6,475,783 as teaching that MAGE-C2 is expressed in about 40% of melanomas (page 40, lines 27 thru page 41, line 1).

The specification cannot be reasonably extrapolated to enable the claims because one of skill in the art could not predict that MAGE-C2 protein is expressed in primary tumor cells and thus one of skill in the art would not know how to use the invention. The teaching in the specification that CTLs reactive with MAGE-C2 peptides were isolated from a single patient, patient EB81, wherein the patient was shown to express a mutated MAGE-C2 gene, is not sufficient to establish that the MAGE-C2 protein is expressed in primary tumors to an extent that one of skill in the art would predictably know how to use the invention. The mutated form contained a mutation in the 5-prime untranslated portion of the gene and the effect of this mutation on protein expression is unknown. In particular, Germeau (2005, The J. of Exp. Med. 201(2):241-248) teaches that a major class of tumor antigens are encoded by genes that are mutated in tumor cells, but that in most cases, they are observed only in a single tumor cell. Thus, because patient EB81 expressed a mutated form of the EB81 gene, one of skill in the art could not predict that this gene would be expressed in primary tumors of other patients.

Further, the teaching in the specification that the isolated CTL clone was reactive with other tumor cell lines is not sufficient to establish that the MAGE-C2 protein is expressed in primary tumors to an extent that one of skill in the art would predictably know how to use the invention. In particular, it is noted that Freshney (Culture of Animal

Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions. Thus, it is not clear whether the expression of MAGE-C2 in the cell lines is an artifact of the cell culture system of the particular neoplastic cell lines or whether this can be in any way related to the *in vivo* cells from which the cell lines were derived in view of the art recognized problems with artifacts associated with cell culture. For example, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*. Thus, based on the cell culture data presented in the specification, in the absence of data provided from primary tumor cells and normal

controls, no one of skill in the art could not predict that the claimed invention would function as contemplated based solely on the cell culture data provided and the single example of a mutated MAGE-C2 gene in a single patient.

Further, references to Lucas et al. (2000, Int. J. Cancer 87:55-60), Gure et al. (2000, Int. J. Cancer 85:726-732), and U.S. Patent No. 6,475,783 in the specification as teaching that MAGE-C2 is expressed in about 40% of melanomas is not sufficient to establish that the MAGE-C2 protein is predictably expressed in primary tumors. A review of these references shows that the analysis of MAGE-C2 expression was an analysis of MAGE-C2 RNA expression. The teaching that MAGE-C2 RNA is expressed in tumor cells is not sufficient to establish that a MAGE-C2 polypeptide is expressed in any primary cancer cells. The prior art is replete with examples in which expression levels of mRNA are not correlated with expression levels of the encoded protein. Brennan et al (Journal of Autoimmunity, 1989, vol. 2 suppl., pp. 177-186) teaches that high levels of the mRNA for TNF-alpha were produced in synovial cells, but that levels of the TNF alpha protein were undetectable, and Zimmer (Cell Motility and the Cytoskeleton, 1991, vol. 20, pp. 325-337) teaches that there is no correlation between the mRNA level of calcium-modulated protein S100 alpha and levels of S100 alpha protein. Eriksson et al. (Diabetologia, 1992, vol. 35, pp. 143-147) teaches that no correlation is observed between levels of mRNA transcripts encoding the insulin-responsive glucose transporter and expression levels of the protein. Thus, observation of mRNA expression does not appear to be predictive of concomitant protein expression. Thus, one of skill in the art could not reliably predict that the MAGE-C2 protein would be expressed in primary tumors based on an analysis of MAGE-C2 RNA expression.

Given the above, one of skill in the art could not predict that the MAGE-C2 protein is expressed in primary tumor cells to the extent required for practice of the invention. Thus, practice of the invention would require undue experimentation.

6. If the above stated rejection were overcome, claims 1-4 and 28-31 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated peptide consisting of the amino acid sequence of ALKDVEERV (SEQ ID NO:3), or a complex comprising an isolated peptide consisting of the amino acid sequence of SEQ ID NO:3, does not reasonably provide enablement for an isolated peptide consisting of an amino acid sequence of ALKDVEERX (SEQ ID NO:1), wherein X is Ala, Leu, Ile, Pro, Phe, Met, Trp, or Glu, or a complex comprising an isolated peptide consisting of an amino acid sequence of ALKDVEERX (SEQ ID NO:1), wherein X is Ala, Leu, Ile, Pro, Phe, Met, Trp, or Glu.

The claims are drawn to the following:

an isolated peptide consisting of an amino acid sequence selected from the group consisting of ALKVEERX (SEQ ID NO:1), wherein X may be an amino acid (claim 1), wherein X is Ala, Val, Leu, Ile, Pro, Phe, Met, Trp or Glu (claim 2), wherein the peptide consists of the amino acid sequence selected from the group consisting of SEQ NO:3 and SEQ ID NO:5 (claim 3),

and

a composition useful in provoking a cytolytic T cell response comprising the isolated peptide of claim 1, and an adjuvant (claim 4),

and

an isolated complex useful in isolating a cytolytic T cell, comprising a first and second binding partner which are specific for each other, wherein said second binding partner is bound a plurality of tetramers of an HLA-A2 molecule, a β_2 microglobulin molecule, and the peptide of claim 1 (claim 28), further comprising a label (claim 29), wherein said first binding partner is avidin and the second binding partner is biotin (claim 30),

and

a composition comprising the tetramer of claim 28 and a carrier (claim 31).

The specification teaches as set forth above. The specification further teaches that changes in the peptide sequence have an effect on the predicted HLA binding affinity (page 26, Table 1).

The teaching of the specification cannot be reasonably extrapolated to enable the scope of the claims because one of skill in the art could not predictably use the peptide of ALKDVEERX (SEQ ID NO:1), wherein X is any amino acid other than valine. The claims encompass peptides wherein X may be amino acids having widely divergent shapes and sizes, and that differ in charge status. Further, the specification teaches that the identity of the X amino acid can significantly affect the predicted HLA binding affinity of the peptide. Further, George et al. (2005, Trends in Immunology 26(12):653-659) teach that the specificity of the interaction with which a T-cell receptor recognizes antigen in the form of a peptide held in the groove of an MHC class molecule is such that a single amino acid substitution in the peptide can abolish the ability of T cells to respond to the antigen or can convert the peptide to an antagonist peptide that "turns off" the ability of a population of T cells to respond by proliferation. Given that the claims are drawn to peptides having terminal amino acids that differ in size, shape, and charge from the exemplified valine, given that the prior art teaches that a single amino acid change in a peptide can be critical in terms of T cell recognition, and given that the specification teaches that the terminal amino acid is predicated to effect HLA binding, one of skill in the art could not predict that peptides having the sequence ALKDVEERX (SEQ ID NO:1), wherein X may be an amino acid other than valine, will be useful in accordance with the invention. Thus, practice of the invention would require undue experimentation.

7. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Catherine Joyce
Examiner
Art Unit 1642